Amendments to the Specification:

Please rewrite the second full paragraph beginning at page 2, line 19, to read as follows:

C1

The most widely recognized monoclonal antibody targeting HER2 receptor function is marketed under the tradename ~~Herceptin®~~ Herceptin® (~~Genetech~~Genentech, Inc., San Francisco, California). This recombinant humanized monoclonal antibody has high affinity for p185HER2. Early clinical trials with patients having extensive metastatic breast carcinomas demonstrate the ability of this monoclonal antibody to inhibit growth of breast cancer cells that overexpress HER2 (Baselga *et al.* (1996) *J. Clin. Oncol.* 14(3):737-744). In one such trial, monotherapy with ~~Herceptin®~~ Herceptin® in metastatic breast cancer patients yielded an overall response rate of 14% (2% complete responders and 12% partial responders). The median duration of response was 9.1 months, median survival was 12.8 months (ranging from 0.5 to 24+ months). Twenty-four percent of the patients were progression free at 5.8 months (Genentech, Inc., data on file). Degree of overexpression of p185HER2 was predictive of treatment effect. In another clinical trial, monotherapy with ~~Herceptin®~~ Herceptin® yielded objective responses in 5 out of 43 assessable metastatic breast cancer patients (11.6%) (as cited in "Cancer and Leukemia Group B (CALGB) 9661, A Pilot Study of Low-dose Interleukin-2 plus Recombinant Human Anti-HER2 Monoclonal Antibody in Solid Tumors"; herein incorporated by reference).

Please rewrite the second paragraph beginning on page 5, line 15, to read as follows:

C2

By "overexpression" of the HER2 receptor protein is intended an abnormal level of expression of the HER2 receptor protein in a cell from a tumor within a specific tissue or organ of the patient relative to the level of expression in a normal cell from that tissue or organ. Patients having a cancer characterized by overexpression of the HER2 receptor can be determined by standard assays known in the art. Preferably overexpression is measured in fixed cells of frozen or paraffin-embedded tissue sections using immunohistochemical (IHC) detection. When coupled with histological staining, localization of the targeted protein can be determined and extent of its expression within a tumor can be measured both qualitatively and semi-quantitatively. Such IHC detection assays are known in the art and include the Clinical Trial Assay (CTA), the commercially available LabCorp 4D5 test, and the commercially

available DAKO HercepTest™ (DAKO, Carpinteria, California). The latter assay uses a specific range of 0 to 3+ cell staining (0 being normal expression, 3+ indicating the strongest positive expression) to identify cancers having overexpression of the HER2 protein (see the ~~Herceptin®~~ Herceptin® (Trastuzumab) full prescribing information; September 1998; Genentech, Inc., San Francisco, California). Thus, patients having a cancer characterized by overexpression of the HER2 protein in the range of 1+, 2+, or 3+, preferably 2+ or 3+, more preferably 3+ would benefit from the methods of therapy of the present invention.

Please rewrite the paragraph beginning at page 9, line 6, to read as follows:

For example, in one embodiment, the therapeutically effective dose of IL-2 (or variant thereof) to be administered concurrently with a pharmaceutical composition comprising at least one anti-HER2 antibody (or fragment thereof), both of which are administered according to a particular dosing regimen, is in the range from about 0.5 ~~mIU/m²~~ MIU/m^2 to about 4.0 ~~mIU/m²~~ MIU/m^2, preferably from about 0.6 ~~mIU/m²~~ MIU/m^2 to about 3.0 ~~mIU/m²~~ MIU/m^2, more preferably from about 0.7 ~~mIU/m²~~ MIU/m^2 to about 2.0 ~~mIU/m²~~ MIU/m^2, even more preferably from about 0.8 ~~mIU/m²~~ MIU/m^2 to about 1.5 ~~mIU/m²~~ MIU/m^2, still more preferably from about 0.9 ~~mIU/m²~~ MIU/m^2 to about 1.25 ~~mIU/m²~~ MIU/m^2, even more preferably about 1.0 ~~mIU/m²~~ MIU/m^2, while the therapeutically effective dose of at least one anti-HER2 antibody or fragment thereof is in the range from about 1.0 mg/kg to about 10.0 mg/kg, preferably about 2.0 mg/kg to about 9.0 mg/kg, more preferably about 3.0 mg/kg to about 8.0 mg/kg, even more preferably about 4.0 mg/kg to about 8.0 mg/kg, still more preferably about 4.0 mg/kg to about 6.0 mg/kg, even more preferably about 4.0 mg/kg. When the amount of IL-2 (or variant thereof) is about 0.8 ~~mIU/m²~~ MIU/m^2 to about 1.5 ~~mIU/m²~~ MIU/m^2 /dose, preferably the total amount of anti-HER2 antibody, which comprises at least one anti-HER2 antibody (or fragment thereof), is about 4.0 mg/kg/dose to about 8.0 mg/kg/dose. Thus, for example, the amount of IL-2 or variant thereof could be about 0.8, 0.9, 1.0, 1.25, or 1.5 ~~mIU/m²~~ MIU/m^2 /dose and the total amount of anti-HER2 antibody could be about 4.0, 5.0, 6.0, 7.0, or 8.0 mg/kg/dose. When the amount of IL-2 or variant thereof is about 1.0 ~~mIU/m²~~ MIU/m^2 /dose, preferably the total amount of anti-HER2 antibody is about 4.0, 5.0, 6.0, 7.0, or 8.0 mg/kg/dose, most preferably about 4.0 mg/kg/dose.

Please amend the paragraph beginning at line 2, page 11, to read as follows:

C4

In yet another embodiment of the invention, the introductory cycle alone or the introductory cycle and at least one subsequent cycle comprising a two-week dosing regimen further comprise intermediate-dose IL-2 pulsing. By "intermediate-dose IL-2 pulsing" is intended the administration of a pharmaceutical composition comprising IL-2 or variant thereof such that an intermediate dose of the IL-2 or variant thereof is given to the subject. By "intermediate dose" is intended an IL-2 dose within the range of about 6.0 ~~mIU/m^2~~ MIU/m^2 to about 16.0 ~~mIU/m^2~~ MIU/m^2, preferably about 8.0 ~~mIU/m^2~~ MIU/m^2 to about 15.0 ~~mIU/m^2~~ MIU/m^2, more preferably about 9.0 ~~mIU/m^2~~ MIU/m^2 to about 14.0 ~~mIU/m^2~~ MIU/m^2, even more preferably about 10.0 ~~mIU/m^2~~ MIU/m^2 to about 13.5 ~~mIU/m^2~~ MIU/m^2, still more preferably about 11.0 ~~mIU/m^2~~ MIU/m^2 to about 13.0 ~~mIU/m^2~~ MIU/m^2, more preferably still about 12.0 ~~mIU/m^2~~ MIU/m^2 IL-2 or variant thereof. Without being bound by theory, administering of intermediate doses of IL-2 further activates effector cells.

Please amend the third paragraph beginning at page 19, line 30, to read as follows:

C5

Examples of pharmaceutical compositions comprising multimeric IL-2 or variants thereof are disclosed in U.S. Patent No. 4,604,377, the disclosure of which is herein incorporated by reference. By "multimeric" is intended the protein molecules are present in the pharmaceutical composition in a microaggregated form having an average molecular association of 10-50 molecules. These multimers are present as loosely bound, physically-associated IL-2 molecules. A lyophilized form of these compositions is available commercially under the tradename ~~Proleukin~~ Proleukin® (Chiron Corporation, Emeryville, California). The lyophilized formulations disclosed in this reference comprise selectively oxidized, microbially produced recombinant IL-2 in which the recombinant IL-2 is admixed with a water soluble carrier such as mannitol that provides bulk, and a sufficient amount of sodium dodecyl sulfate to ensure the solubility of the recombinant IL-2 in water. These compositions are suitable for reconstitution in aqueous injections for parenteral administration and are stable and well tolerated in human patients. When reconstituted, the IL-2 or variants thereof retains its multimeric state. Such

C5 Cont'd

lyophilized or liquid compositions comprising multimeric IL-2 or variants thereof are encompassed by the methods of the present invention. Such compositions are referred to herein as multimeric IL-2 pharmaceutical compositions.

Please replace the first full paragraph beginning at page 23, line 3, to read as follows:

C6

Humanized anti-HER2 antibodies are also encompassed by the term anti-HER2 antibody as used herein. By "humanized" is intended forms of anti-HER2 antibodies that contain minimal sequence derived from non-human immunoglobulin sequences. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. See, for example, U.S. Patent Nos. 5,225,539; 5,585,089; 5,693,761; 5,693,762; 5,859,205; herein incorporated by reference. In some instances, framework residues of the human immunoglobulin are replaced by corresponding non-human residues (see, for example, U.S. Patents 5,585,089; 5,693,761; 5,693,762). Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance (e.g., to obtain desired affinity). In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details see Jones *et al.* (1986) *Nature* 331:522-525; Riechmann *et al.* (1988) *Nature* 332:323-329; and Presta (1992) *Curr. Op. Struct. Biol.* 2:593-596; herein incorporated by reference. One such humanized anti-HER2 antibody is commercially available under the tradename ~~Herceptin®~~ Herceptin® (Genentech, Inc., San Francisco, California).

Please amend the first full paragraph beginning at page 24, line 3, to read as follows:

Fragments of the anti-HER2 antibodies are suitable for use in the methods of the invention so long as they retain the desired affinity of the full-length antibody. Thus, a fragment of an anti-HER2 antibody will retain the ability to bind to the ~~CD20 B-cell surface antigen~~HER2 receptor protein. Fragments of an antibody comprise a portion of a full-length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include, but are not limited to, Fab, Fab' $F(ab')_2$, and Fv fragments and single-chain antibody molecules. By "single-chain Fv" or "sFv" antibody fragments is intended fragments comprising the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. See, for example, U.S. Patent Nos. 4,946,778; 5,260,203; 5,455,030; 5,856,456; herein incorporated by reference. Generally, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun (1994) in *The Pharmacology of Monoclonal Antibodies*, Vol. 113, ed. Rosenburg and Moore (Springer-Verlag, New York), pp. 269-315.

Please amend the paragraph beginning at page 27, line ~~25~~ 18 to read as follows:

Meropol *et al.* (reference 5 of the CALGB 9661 Protocol) have demonstrated that PBMC may be expanded several fold *in vivo* with daily subcutaneous administration of IL-2, at doses that result in 10-100 pM peak levels with minimal toxicity. The maximum tolerated dose in this study was 1.25 ~~mIU/m^2~~ MIU/m^2 daily. At daily doses ranging from 0.4-1.5 ~~mIU/m^2~~ MIU/m^2, NK cell expansion from 154-530% above baseline was observed. In an effort to stimulate the cytotoxic mechanism in this expanded population, Meropol and Caligiuri (unpublished data) have administered 10-fold higher doses of IL-2 as outpatient pulses subcutaneously for three days every two weeks in patients receiving daily low-dose treatment. The maximum-tolerated "intermediate-dose" pulse in this schedule is 15 ~~mIU/m^2~~ MIU/m^2. The intermediate-dose pulsing further augmented NK expansion *in vivo*. For patients treated with escalating intermediate pulse doses every two weeks, NK cell number rose from 226/μl to greater than 1,500/μl after pulsing. Dose-limiting toxicities with both low-dose IL-2 and intermediate-dose pulsing have been largely constitutional, with fever, chills, and fatigue predominating. Severe side effects observed with high-dose IL-2, such as capillary leak syndrome, renal failure, and

C8 Cont'd

hypotension requiring pressors did not occur. Thus, IL-2 doses capable of engaging intermediate affinity receptors (and hence stimulating effector cell cytotoxicity) may be safely administered to outpatients with expanded NK populations in repetitive fashion.

Please amend the first paragraph beginning at page 29, line 2, to read as follows:

C9

The IL-2 formulation used in this study is manufactured by Chiron Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin, which differs from the native human IL-2 sequence in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by a serine residue (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from *E. coli*, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543. The IL-2 formulation marketed as ~~Proleukin~~ Proleukin® is supplied as a sterile, white to off-white preservative-free lyophilized powder in vials containing 1.3 mg of protein (22 MIU).

Please amend the second paragraph beginning at page 29, line 12, to read as follows:

C10

The anti-HER antibody administered in this study is commercially available as ~~Herceptin®~~ Herceptin® (Trastuzumab; ~~Genetech~~Genentech, Inc., San Francisco, California). ~~Herceptin®~~ Herceptin® is a recombinant humanized monoclonal antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. The humanized antibody against HER2 is produced by a mammalian cell (Chinese hamster ovary (CHO)) suspension culture in a nutrient medium containing the antibiotic gentamicin. This antibiotic is not detectable in the final product.

Please amend the third paragraph beginning at page 29, line 21, to read as follows:

C11

~~Herceptin®~~ Herceptin® is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The nominal content of each ~~Herceptin®~~ Herceptin® vial is 440 mg Trastuzumab, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, 400 mg αα-trehalose dihydrate, and 1.8 mg polysorbate 20, USP.

Please amend the paragraph beginning at page ~~30~~ 29-27, line ~~3~~, to read as follows:

C12

This study, which was coordinated by the Cancer and Leukemia Group B (CALGB Protocol 9661) was activated April 15, 1997, and closed March 3, 2000. The aims of this pilot study were to determine the toxicity, immunologic effects, and anti-tumor effect of the combination of IL-2 and humanized anti-HER2 monoclonal antibody. It should be noted that the IL-2 doses used in the 1.0, 2.0, and some of the 4.0 mg/kg antibody dose cohorts were 1.25 million international units (~~mIU~~ MIU)/m^2 for the low-dose and 15.0 ~~mIU/m²~~ MIU/m^2 for the intermediate-dose IL-2 pulse.

Please amend the two successive paragraphs beginning at page 32, lines 6-20, to read as follows:

C13

Patients received an introductory cycle (cycle 1) during which low-dose IL-2 (1.0 ~~mIU/m²~~ MIU/m^2) was administered daily by subcutaneous injection on days 1-7 and days 11-20, and intermediate-dose IL-2 pulsing (12.0 ~~mIU/m²~~ MIU/m^2 administered by subcutaneous injection) occurred on days 8-10. During this cycle, humanized anti-HER2 antibody was administered as a single 90-minute IV infusion before administration of the low-dose IL-2 on day 7 of cycle 1 and 24 hours before intermediate-dose pulsing, to determine toxicity with low-dose IL-2 alone.

Patients then received one or more subsequent cycles, each lasting for 14 days, during which humanized anti-HER2 antibody was administered as a single 90-minute IV infusion on day 1 prior to intermediate-dose IL-2 pulsing (12.0 ~~mIU/m²~~ MIU/m^2) on that same day and days 2 and 3 of this cycle. Low dose IL-2 (1.0 ~~mIU/m²~~ MIU/m^2) was then administered daily by subcutaneous injection on days 4-14. This 14-day cycle was repeated until disease progression or

C 13 Cont'd

until the patient was taken off protocol treatment. For one antibody dose level (8.0 mg/kg), the antibody was also administered biweekly during the 14-day cycles.

Please amend the paragraph beginning on page 36, line 19, to read as follows:

C 14

At this point, the protocol was amended to new IL-2 doses of 1.0 ~~mIU/m^2~~ MIU/m^2 for the low-dose and 12 ~~mIU/m^2~~ MIU/m^2 for the intermediate pulse. Five patients accrued to a 4.0 mg/kg antibody dose level cohort with the new IL-2 doses. None required IL-2 dose reductions. One patient experienced an antibody DLT experiencing respiratory distress upon receiving the first dose of antibody. One patient achieved a complete response after 2 cycles and ended treatment to receive non-protocol HER2. The remaining 3 patients achieved a level of response (2 PRs, 1 SD), and remained on treatment until progressive disease occurred after 14, 10, and 8 cycles, respectively.

Please amend the second full paragraph beginning at page 37, lines 13, to read as follows:

C 15

In summary, 33 out of the 45 patients were breast cancer patients. Of the 6 patients showing a positive response to combination therapy, all were breast cancer patients. Thus approximately 18% of the breast cancer patients were positive responders across all treatment levels. This compares favorably with historical data for breast cancer patients receiving monotherapy with ~~Herceptin®~~ Herceptin®, where overall response rate was 11.6% (as quoted in the CALGB 9661 Protocol) and 14% (~~Genetech~~Genentech, Inc., data on file) in clinical trials.